



**VI CONGRESO LATINOAMERICANO
DE BIOQUÍMICA CLÍNICA**

**II CONGRESO INTERNACIONAL DEL
COLEGIO NACIONAL DE BACTERIOLOGÍA**

¡El riesgo es que te quieras quedar!

Cartagena, Colombia 3 al 6 OCTUBRE 2024

New Tools for Detecting and Reducing Error in the Total Testing Process

Post-Analytical: Choosing the right reference intervals!

A Case Series

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Case 1: Complaints of Too Many High Calcium Results

- The laboratory director received a complaint from a group of physicians who recently joined their health system. They were concerned that they are seeing too many abnormal high calcium results.
- The director requested data on the percentage of high abnormal calcium results by location so they can investigate this further.

Case 1: Complaints of Too Many High Calcium Results

- The data analyst provided the following results for the health system (excluded sites with less than 60 collections/month), ranked by % high Calciums:

Location	# High	# OK	Grand Total	% High
PED Bld Draw WP2	57	282	339	16.8%
Draw St. PED Wharf	62	324	386	16.1%
Orange Draw St.	51	276	327	15.6%
PED Treatment Center	12	68	327	15.6%

- 3 out of top 4 are pediatric locations. What's going on?

Case 1: Complaints of Too Many High Calcium Results

- Site was using a single reference interval designed for adults:
8.8 – 10.2 mg/dL (Roche)
- For pediatric patients, recent pediatric reference interval studies recommend:
 - <1 yr: 8.7 – 11.0 mg/dL
 - 1-17 yr: 9.3 – 10.6 mg/dL
- This means for some pediatric patients, results that should be considered normal for their age group, are flagged as high by the laboratory based on adult ranges

Estey MP, Cohen AH, Colantonio DA, et al. *Clin Biochem.* 2013;1197-1219.

Case 1: Recommendation: Apply Pediatric Reference Intervals

- Without pediatric reference intervals, you may be misinterpreting results
- Assay manufacturers often do not provide pediatric reference intervals, so laboratory directors need to consult published literature that are specific to their assay
 - I recommend consulting CALIPER published studies who evaluated reference intervals for common chemistry tests in over 10,000 healthy children

Estey MP, Cohen AH, Colantonio DA, et al. *Clin Biochem.* 2013;1197-1219.

Lesson 1: Implement age-specific reference intervals



Case 2: Complaints of Too Many Low Total Protein Results

- The laboratory director received a complaint from a hospitalist at an affiliated clinic. They were concerned that they are seeing too many abnormal low protein and globulin results.
- The director requested specific patient examples to review and evaluate.

Case 2: Complaints of Too Many Low Total Protein Results

Total Protein	Ref Range	Albumin	Ref Range	Globulin	Ref Range	Tube
6.3	6.6 - 8.7	4.1	3.6 - 4.9	2.2	2.3 - 3.5	Serum (gold top)
6.4	6.6 - 8.7	4.2	3.6 - 4.9	2.2	2.3 - 3.5	Plasma (green top)
6.8	6.6 - 8.7	4.7	3.6 - 4.9	2.1	2.3 - 3.5	Serum (gold top)
6.5	6.6 - 8.7	4.7	3.6 - 4.9	1.8	2.3 - 3.5	Serum (gold top)
6.8	6.6 - 8.7	5.0	3.6 - 4.9	1.8	2.3 - 3.5	Serum (gold top)
6.9	6.6 - 8.7	4.8	3.6 - 4.9	2.1	2.3 - 3.5	Serum (gold top)
6.0	6.6 - 8.7	4.4	3.6 - 4.9	1.6	2.3 - 3.5	Serum (gold top)
6.7	6.6 - 8.7	4.8	3.6 - 4.9	1.9	2.3 - 3.5	Serum (gold top)

Case 2: Complaints of Too Many Low Total Protein Results

- Studies confirm that serum has 10-20% lower total protein than plasma
- No such data exists for globulin

Case 2: Complaints of Too Many Low Total Protein Results

Expected values

Expected values according to Josephson⁹

Adults	66-87 g/L	(6.6-8.7 g/dL)
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Expected values according to Tietz¹⁰

Umbilical cord	48-80 g/L	(4.8-8.0 g/dL)
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Premature	36-60 g/L	(3.6-6.0 g/dL)
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Newborn	46-70 g/L	(4.6-7.0 g/dL)
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1 week	44-76 g/L	(4.4-7.6 g/dL)
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7 months-1 year	51-73 g/L	(5.1-7.3 g/dL)
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1-2 years	56-75 g/L	(5.6-7.5 g/dL)
-----------	-----------	----------------

> 3 years	60-80 g/L	(6.0-8.0 g/dL)
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Adults (ambulatory)	64-83 g/L	(6.4-8.3 g/dL)
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Expected values according to Australasian Association of Clinical Biochemists¹¹

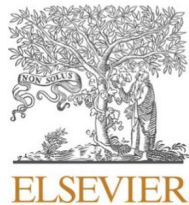
Adults	60-80 g/L
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Lesson 2: Manufacturer product inserts are not always helpful or up-to-date!



Case 2: Complaints of Too Many Low Total Protein Results

Clinica Chimica Acta 562 (2024) 119851



Contents lists available at [ScienceDirect](#)

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca



Accounting for differences between serum and plasma: An indirect approach to derive reference intervals for total protein, albumin, and globulin

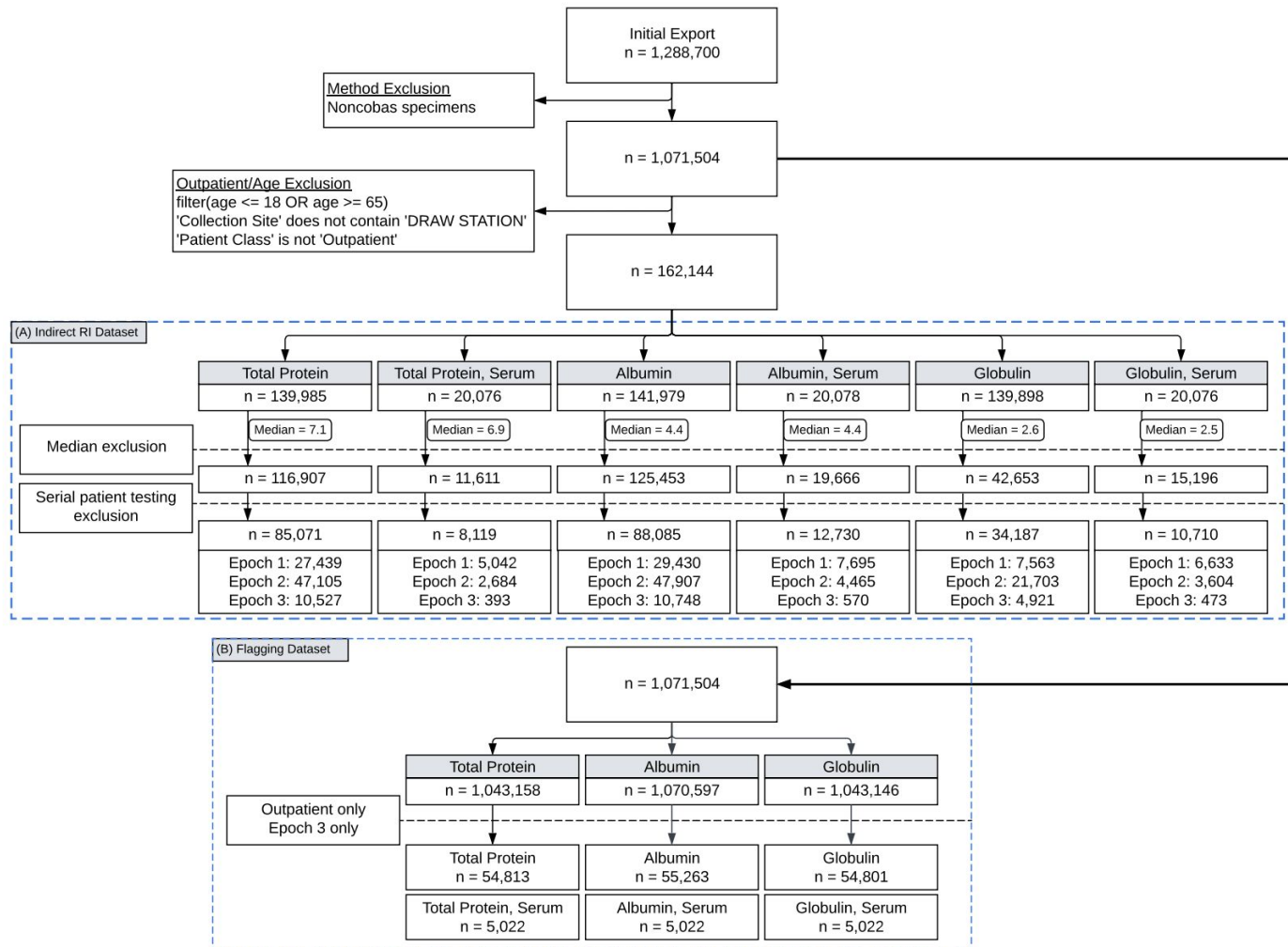


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Case 2: Complaints of Too Many Low Total Protein Results



Case 2: Complaints of Too Many Low Total Protein Results

5.9 to 8.3 g/dL (New)

Total Protein

Total Protein,
Serum

6.6 to 8.7 g/dL

(Historical)

Total Protein

Total Protein,
Serum

3.6 to 5.1 g/dL (New)

Albumin

Albumin, Serum

3.6 to 4.9 g/dL

(Historical)

Albumin

Albumin, Serum

1.9 to 3.9 g/dL (New)

Globulin

Globulin, Serum

2.3 to 3.5 g/dL

(Historical)

Globulin

Globulin, Serum

Lesson 3: Consider differences that can exist due to pre-analytical process



Case 3: Levothyroxine Overprescriptions

Yale SCHOOL OF MEDICINE

≡ MENU

21 Million Americans May Take a Hypothyroidism Drug They Don't Need

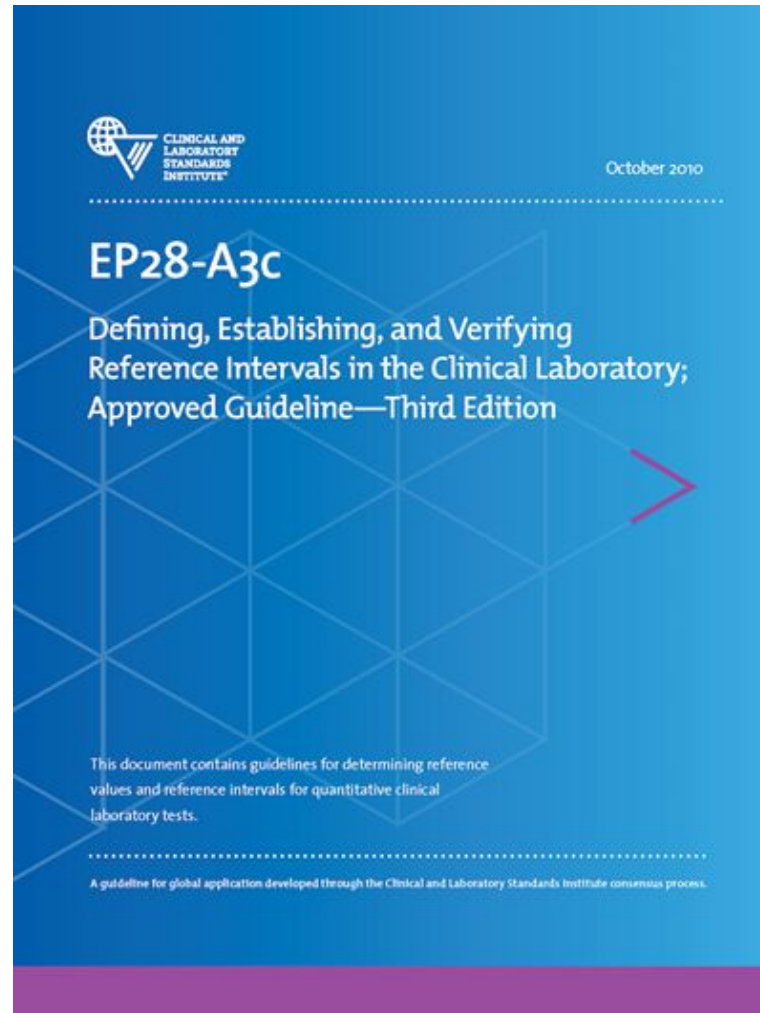
March 31, 2023

by Isabella Backman

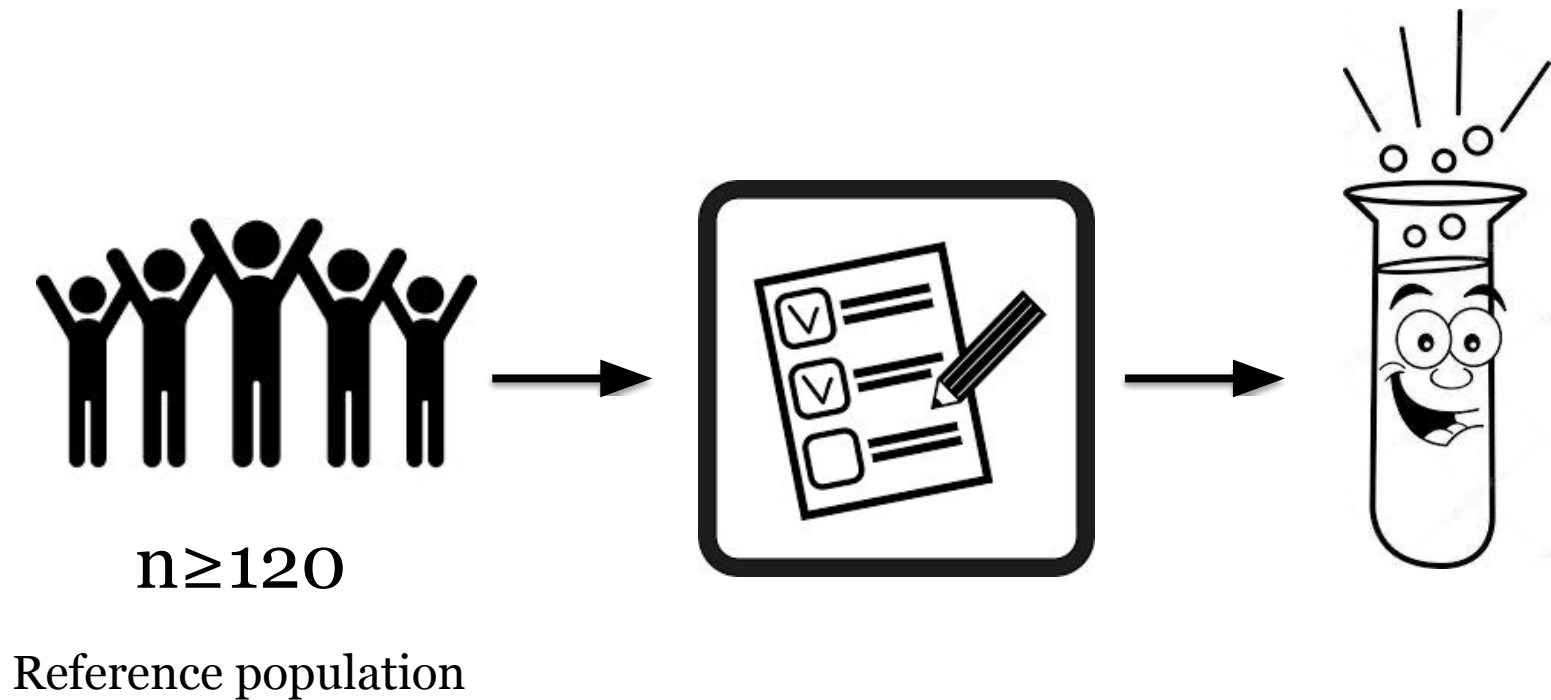
How do you derive a reference interval for a new test X?



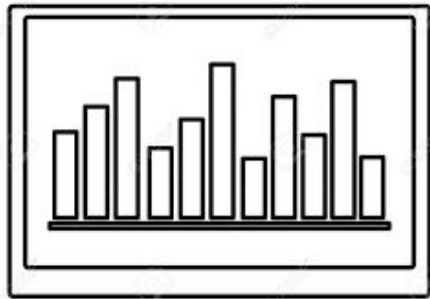
Introducing CLSI EP28-A3C



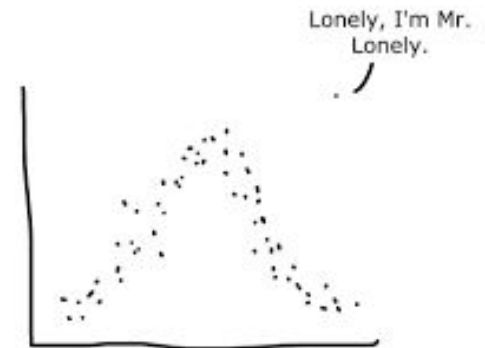
Introducing CLSI EP28-A3C



Introducing CLSI EP28-A3C

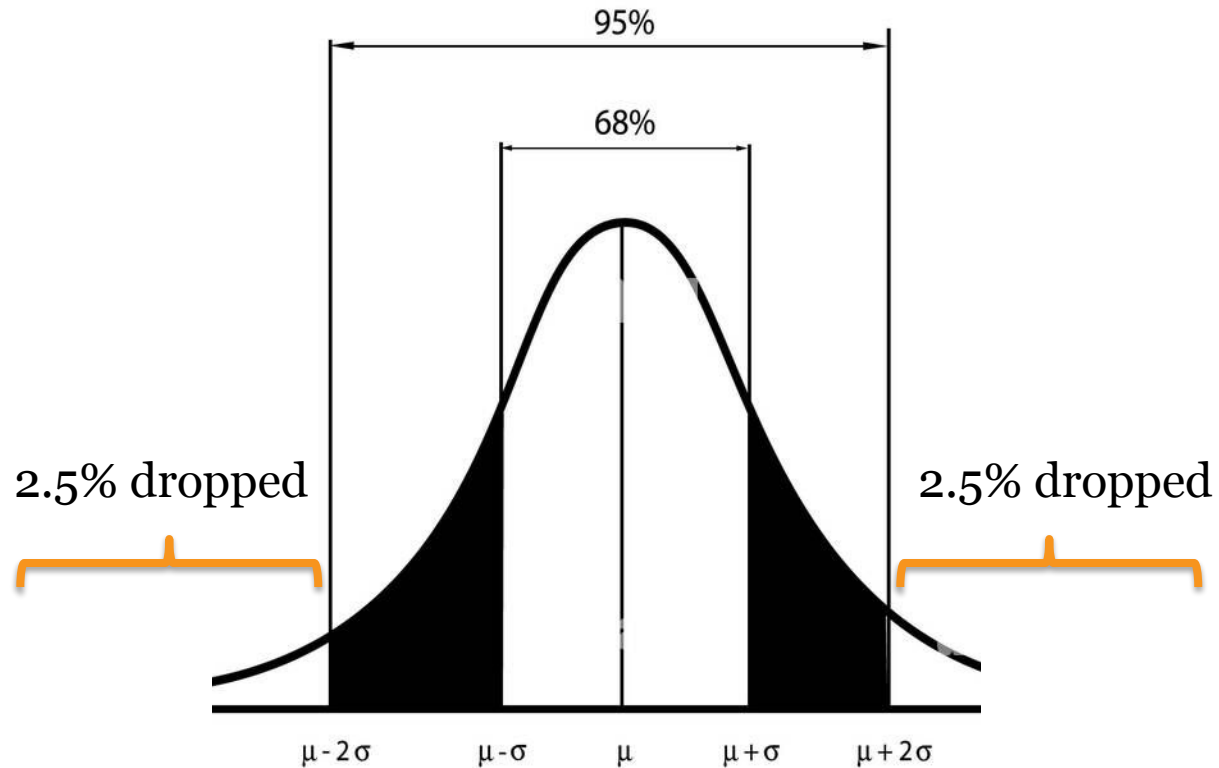


Rank	Value
1	0.10
2	0.12
3	0.23
...	
...120	5.6



Outlier Elimination

Introducing CLSI EP28-A3C



Reference Interval for X = 0.27 – 4.2 mIU/L

Lesson Learned

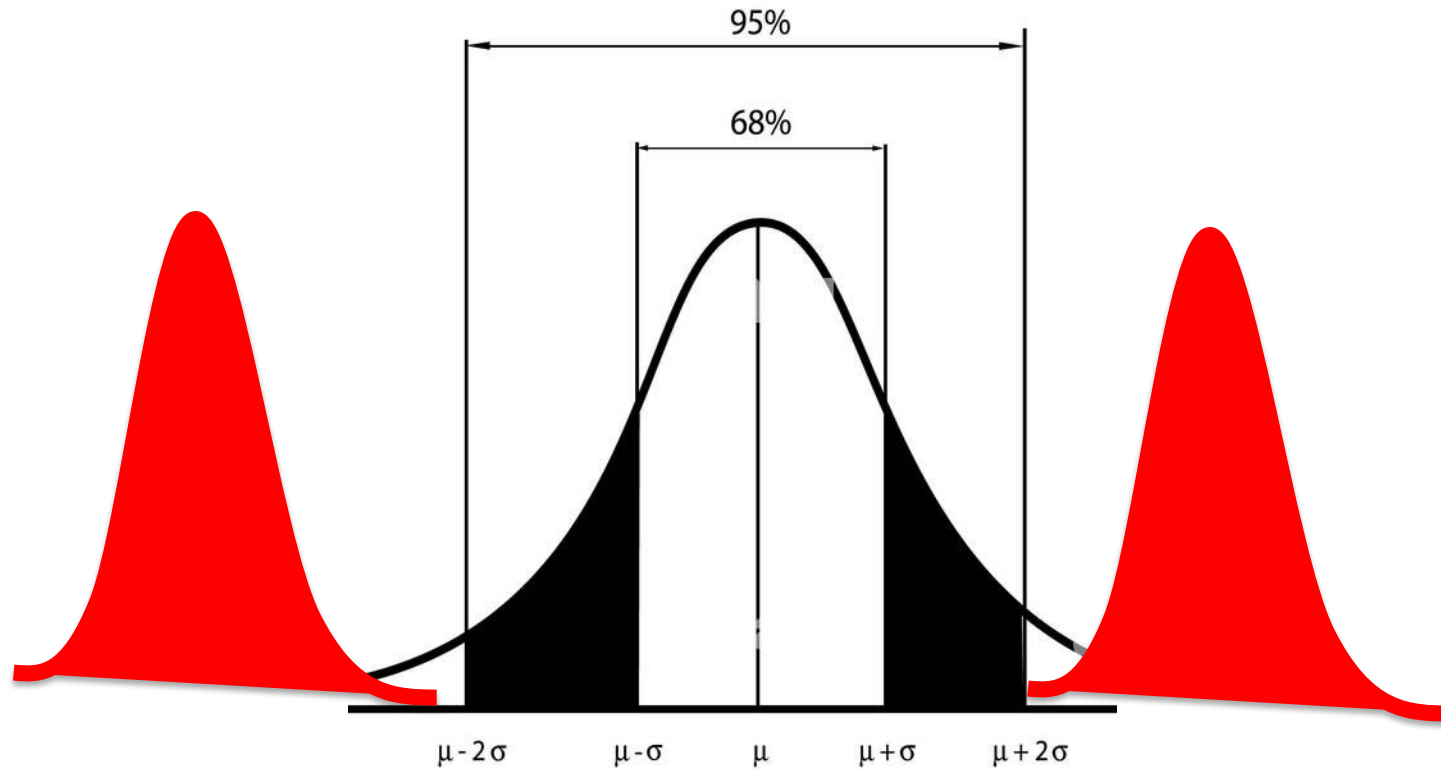
Current reference intervals will flag **abnormal** for
~5% of **healthy** population



That's crazy!!
Why are we doing that?



Introducing Disease



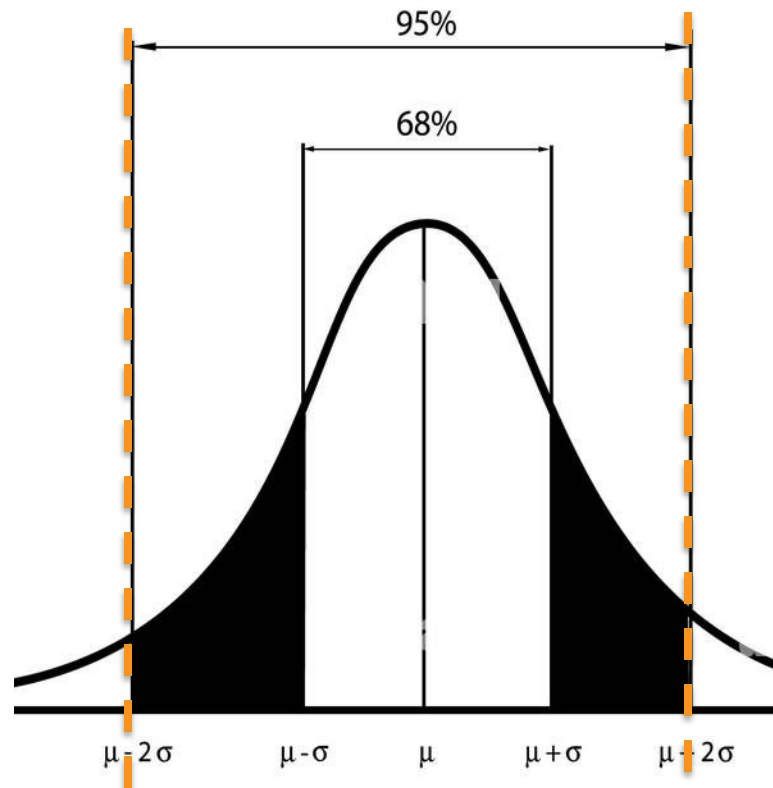
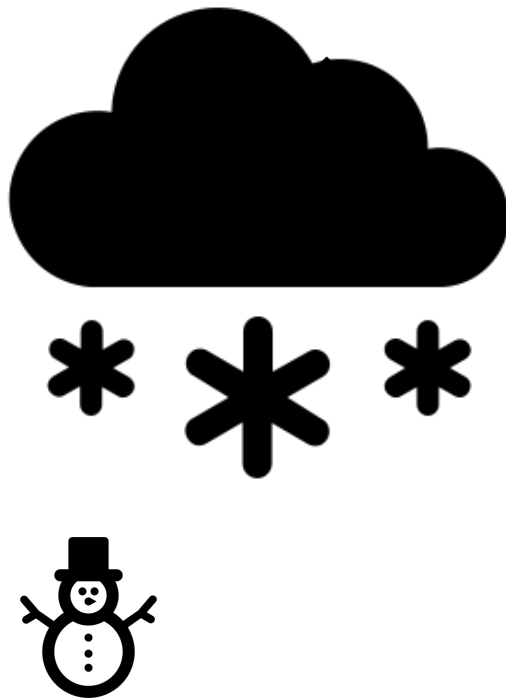
Reference Interval for X = 0.27 – 4.2 mIU/L

Lesson Learned

For most tests, reference intervals are based
SOLELY on data from the reference population.



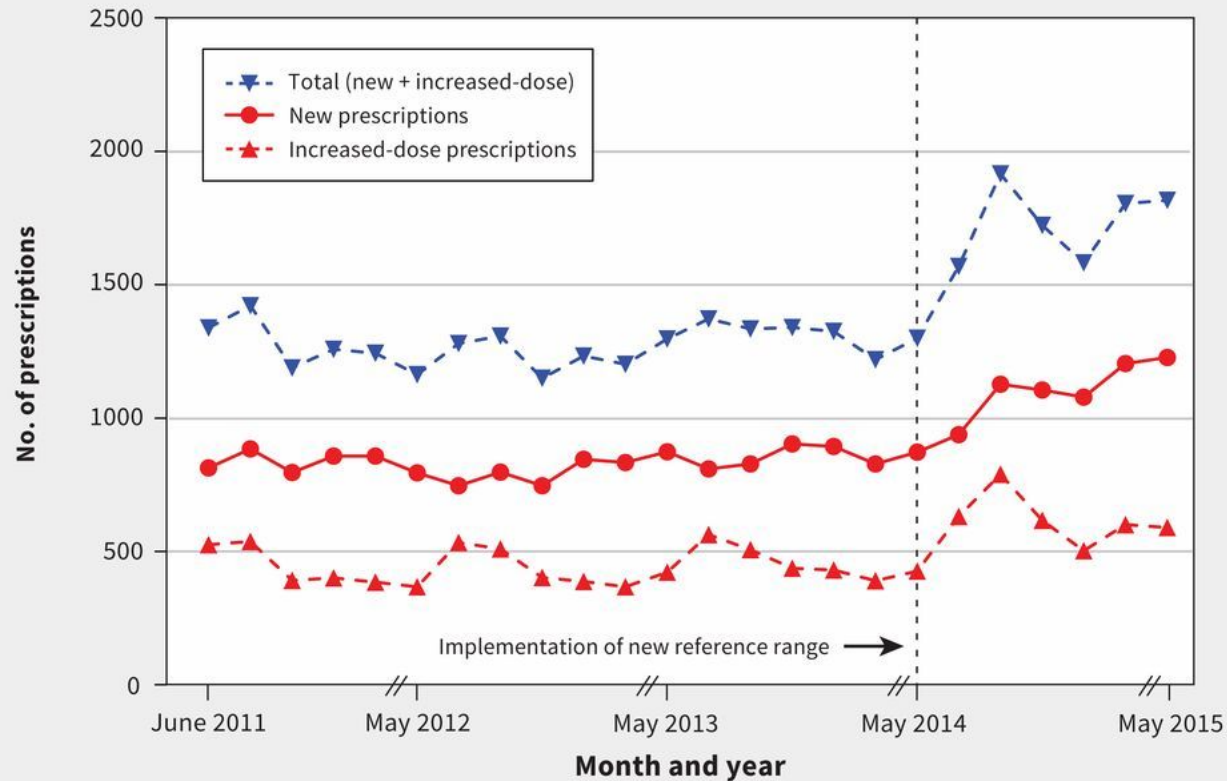
Introducing “Unaccounted Variables”: Season



Reference Interval for TSH = 0.27 – 4.2 mIU/L

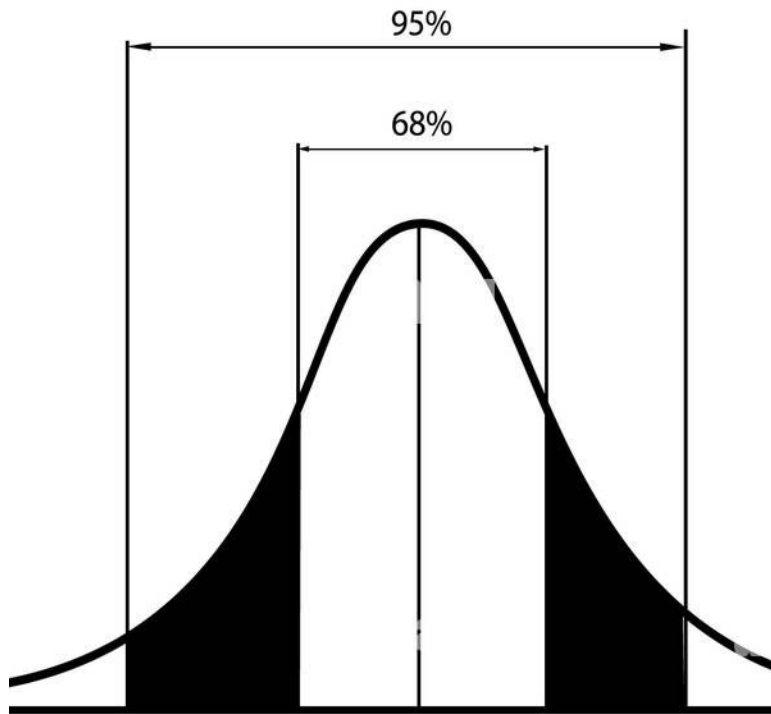


Upper RI and Levo Prescriptions



1. El-Khoury JM. *Clin Chem.* 2023;69:537-538.
2. Symonds C et al. *CMAJ.* 2020;192:E469-475.

Decision Point



TSH (Final result)

	Value	Range
Thyroid Stimulating Hormone Male & Non-pregnant Females: 0.270-4.200 $\mu\text{IU/mL}$ 1st Trimester: 0.110-3.480 $\mu\text{IU/mL}$ 2nd Trimester: 0.320-3.850 $\mu\text{IU/mL}$ As TSH is known to naturally increase in winter, with age and due to certain non-thyroidal illnesses, please consider retesting adults with mild abnormalities (ie, TSH <10 $\mu\text{IU/mL}$) after 2-3 months prior to initiating therapy.	5.800 (H)	See Comment $\mu\text{IU/mL}$

Lesson 4: Decisions on reference intervals can have a major impact on patient care



Changing Reference Interval Paradigm

JOURNAL ARTICLE

Seasonal Variation and Thyroid Function Testing: Source of Misdiagnosis and Levothyroxine Over-Prescription FREE

Joe M El-Khoury ✉

Clinical Chemistry, Volume 69, Issue 5, May 2023, Pages 537–538,
<https://doi.org/10.1093/clinchem/hvad017>

Published: 01 March 2023 **Article history** ▼

JOURNAL ARTICLE

Time to Reevaluate the 95% Inclusion Criteria for Defining Reference Intervals?

Joe M El-Khoury ✉, Tony Badrick, Elvar Theodorsson

Clinical Chemistry, hvae026, <https://doi.org/10.1093/clinchem/hvae026>

Published: 18 March 2024 **Article history** ▼

For more information



The video player displays a man with glasses and a brown jacket speaking. In the top left corner of the video frame, there is a graphic with the text "LEVOTHYROXINE OVERPRESCRIPTIONS" overlaid on a blue, particle-like background. The video player controls at the bottom show the "Yale" logo, a progress bar at 13:00 / 14:24, and various playback icons.

Episode 10: Ending Levothyroxine Overprescriptions



Similarly for ALT: They did not account for alcohol!






Clinica Chimica Acta
Volume 526, 1 February 2022, Pages 62-65



The ALT upper reference interval debate: Blame it on the alcohol

Michael A. Vera^a, Christopher D. Koch^a, AnnMarie Liapakis^b, Joseph K. Lim^c,
Joe M. El-Khoury^a  

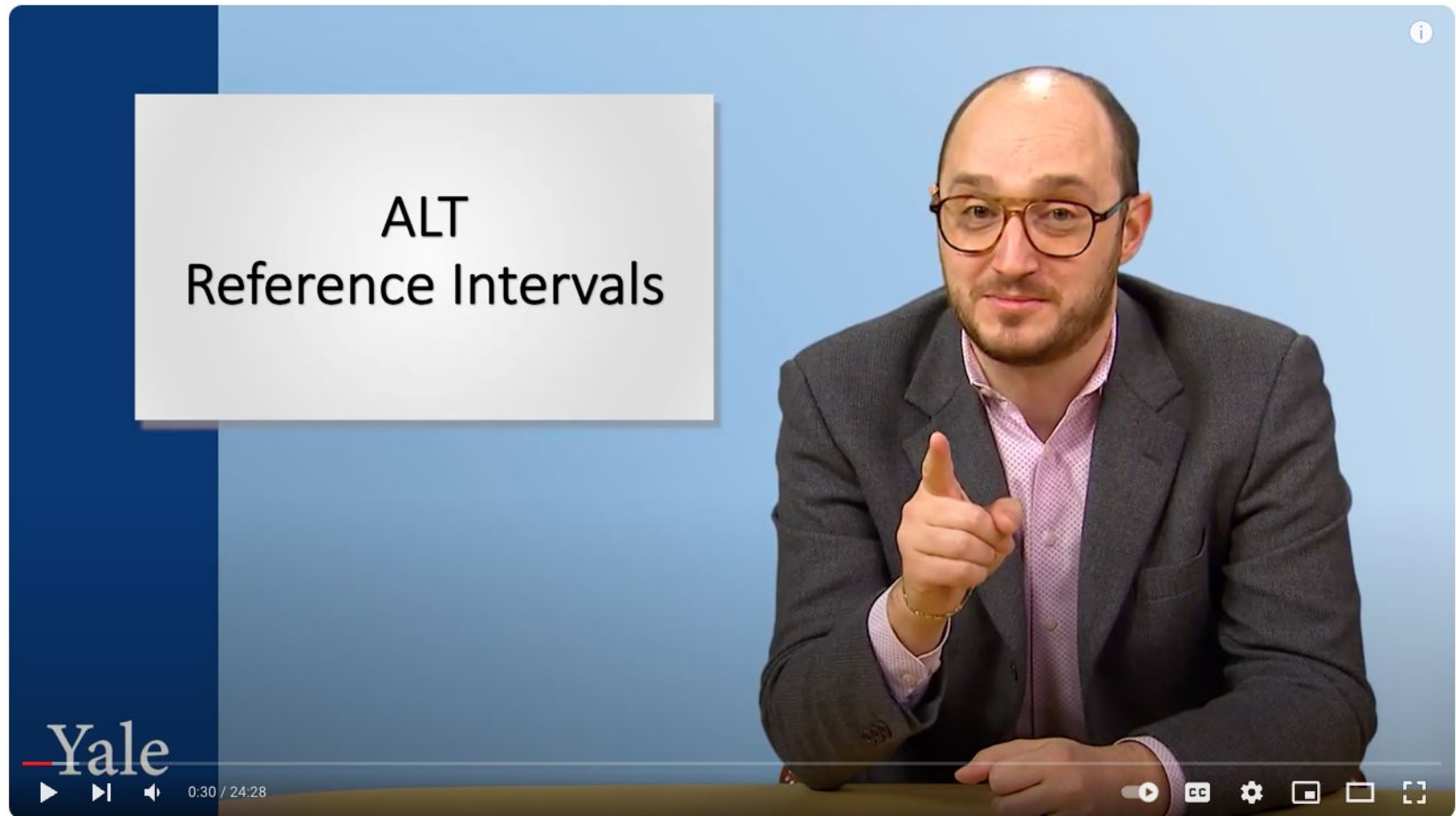
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<https://doi.org/10.1016/j.cca.2021.12.026> 

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For more information



A video player interface showing a man in a suit and glasses pointing towards a slide. The slide is white with the text "ALT Reference Intervals" in black. The video player includes a progress bar at the bottom left showing "0:30 / 24:28" and the Yale logo. On the bottom right, there are icons for play, volume, closed captions, settings, and full screen.

Episode 3: Fixing ALT Reference Intervals

Lesson 1: Implement
age-specific reference intervals

Lesson 2: Consider differences that can
exist due to pre-analytical process

Lesson 3: Manufacturer product inserts
are not always helpful or up-to-date!

Lesson 4: Decisions on reference
intervals can have a major impact on
patient care





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